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PATENT COOPERATION TREATY

PCT

NOTIFICATION CONCERNING
AMENDMENTS OF THE CLAIMS(PCT Rule 62 and
Administrative Instructions, Section 417)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

Date of mailing:

23 March 1998 (23.03.98)

in its capacity as International Preliminary Examining Authority

International application No.:

PCT/US97/12677

International filing date:

18 July 1997 (18.07.97)

Applicant:

THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK et al

The International Bureau hereby informs the International Preliminary Examining Authority that no amendments under Article 19 have been received by the International Bureau (Administrative Instructions, Section 417)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorised officer:

M. Fourne-Godbersen

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 23 March 1998 (23.03.98)	
International application No. PCT/US97/12677	Applicant's or agent's file reference 48962-A-PCT
International filing date (day/month/year) 18 July 1997 (18.07.97)	Priority date (day/month/year) 22 July 1996 (22.07.96)
Applicant SATO, Taka-Aki et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

19 February 1998 (19.02.98)

☐ in a notice effecting later election filed with the International Bureau on:
2. The election ☒ was
☐ was not

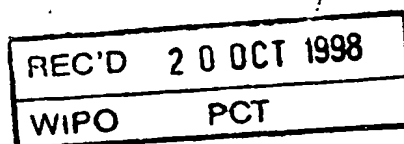
made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer M. Fourne-Godbersen Telephone No.: (41-22) 338.83.38
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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference 48962-A-PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US97/12677	International filing date (day/month/year) 18 JULY 1997	Priority date (day/month/year) 22 JULY 1996
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 19 FEBRUARY 1998	Date of completion of this report 24 AUGUST 1998
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer YVONNE EYLER
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US97/12677

I. Basis of the report

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments):*

- ☒ the international application as originally filed.
- ☒ the description, pages 1-61 , as originally filed.
pages NONE , filed with the demand.
pages NONE , filed with the letter of _____
pages _____ , filed with the letter of _____
- ☒ the claims, Nos. 1-120 , as originally filed.
Nos. NONE , as amended under Article 19.
Nos. NONE , filed with the demand.
Nos. NONE , filed with the letter of _____
Nos. _____ , filed with the letter of _____
- ☒ the drawings, sheets/fig 1-26 , as originally filed.
sheets/fig NONE , filed with the demand.
sheets/fig NONE , filed with the letter of _____
sheets/fig _____ , filed with the letter of _____

2. The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE
- ☒ the claims, Nos. NONE
- ☒ the drawings, sheets/fig NONE

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US97/12677

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. STATEMENT**

Novelty (N)	Claims	<u>(Please See supplemental sheet)</u>	YES
	Claims	<u>(Please See supplemental sheet)</u>	NO
Inventive Step (IS)	Claims	<u>(Please See supplemental sheet)</u>	YES
	Claims	<u>(Please See supplemental sheet)</u>	NO
Industrial Applicability (IA)	Claims	<u>(Please See supplemental sheet)</u>	YES
	Claims	<u>(Please See supplemental sheet)</u>	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-6, 25, 26, 27-39, 48, 52-66, 73, 117-120 lack novelty under PCT Article 33(2) as being anticipated by Matsumine et al (Science 272:1020-1023, 1996) as evidenced by Doyle et al. (Cell 85:1067-1076, 1996).

Matsumine et al disclose a composition, a synthetic peptide corresponding to the COOH-terminal 15 amino acids of APC, which inhibits binding between the signal transduction protein, APC and the cytoplasmic protein DLG which contains a GLGF repeat. (See the abstract, page 1020, column 2; page 1021). Matsumine et al do not specifically address the content of the C-terminal amino acids of the signal transduction protein or the synthetic peptide as containing S/T/-X-V/I/L, however, it would be inherent that said C-terminal amino acids contain the sequence S/T-X-V/I/L because it was known in the art that these three C-terminal amino acids are critical for PDZ binding as evidenced by Doyle et al (page 1073, column 2, first two paragraphs). Matsumine et al. further disclose methods of identifying the peptide compositions both in vivo and in vitro, by detecting disruption of binding (See page 1020, column 2 into 1021, column 1).

Claims 1-120 lack an inventive step under PCT Article 33(3) as being obvious over Matsumine et al. as evidenced by Doyle et al as set forth above and further in view of YEDA RESEARCH AND DEVELOPMENT CO. LTD (WO 96/18641) and Zhang et al. (Molecular Cell Biol. 16:2756-2763, 1996).

Matsumine et al disclose as set forth above but do not disclose disruption of binding to Fas, disruption of signal transduction by such binding, and treatment of cancer or virally infected cells by administration of said peptides to induce apoptosis. Matsumine et al, do teach the role that binding of APC to PDZ domain containing proteins plays in signal transduction. YEDA...and Zhang et al disclose the binding of APC by Fas, it's role in inducing apoptosis, screening of peptides which disrupt said binding at multiple domains, and the use of said peptides to modulate signal transduction and to induce apoptosis in cells, such as tumor cells or virally infected cells. See YEDA, pages 7-13 and Zhang, the entire article).
(Continued on Supplemental Sheet.)

VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to adequately enable practice of the claimed invention because: The description discloses the identification of peptides that interrupt binding between APC and Fas. There is no objective evidence regarding binding between any other protein and Fas and there is insufficient objective evidence supplied to render it predictable that the administration of such proteins would be reasonably expected to target to the appropriate location and effect apoptosis in cancer or virally infected cells and thus effectively treat the disease.

Claims 43-47, 49, 68-72, 74, and 89-100 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not enabled as required under PCT Rule 5.1(a) for the reasons set forth in the immediately preceding paragraph.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US97/12677

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(6): A61K 38/00, 39/00; C07K 1/00, 14/00, 17/00; G01N 33/53, 33/567, 33/574 and US Cl.: 424/198.1; 514/2; 530/351; 435/7.1, 7.23

V. 1. REASONED STATEMENTS:

The report as to Novelty was positive (YES) with respect to claims 7-24, 40-47, 49-51, 67-72, 74-116.

The report as to Novelty was negative (NO) with respect to claims 1-6, 25, 26, 27-39, 48, 52-66, 73, 117-120.

The report as to Inventive Step was positive (YES) with respect to claims NONE.

The report as to Inventive Step was negative (NO) with respect to claims 1-120.

The report as to Industrial Applicability was positive (YES) with respect to claims 1-120.

The report as to Industrial Applicability was negative (NO) with respect to claims NONE.

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

Claims 7-24, 40-47, 49-51, 67-72, 74-116 meet the criteria set out in PCT Article 33(2), because the does not explicitly disclose identification of peptides which induce apoptosis by APC/Fas interactions their use in the treatment of cancer and viral infection.

Claims 1-120 meet the criteria set out in PCT Article 33(4), because the identification of peptides which induce apoptosis by APC/Fas interactions would be useful in the treatment of cancer and viral infection.

_____**NEW CITATIONS**_____

NONE

7

Let-See

E-K

69/230111

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 01 OCT 1999

WIPO PCT

Applicant's or agent's file reference 48962-A-PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US97/12677	International filing date (day/month/year) 18 JULY 1997	Priority date (day/month/year) 22 JULY 1996
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets.
☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

**CORRECTED
VERSION**

Date of submission of the demand 19 FEBRUARY 1998	Date of completion of this report 24 AUGUST 1998
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer YVONNE EYLER Telephone No. (703) 308-0196 JOYCE BRIDGERS PARALEGAL SPECIALIST CHEMICAL MATRIX <i>JKB</i>

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US97/12677

I. Basis of the report

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments).*

☒ the international application as originally filed.

☒ the description, pages 1-61 , as originally filed.

pages NONE , filed with the demand.

pages NONE , filed with the letter of _____.

pages _____ , filed with the letter of _____.

☒ the claims, Nos. 1-120 , as originally filed.

Nos. NONE , as amended under Article 19.

Nos. NONE , filed with the demand.

Nos. NONE , filed with the letter of _____.

Nos. _____ , filed with the letter of _____.

☒ the drawings, sheets/fig 1-26 , as originally filed.

sheets/fig NONE , filed with the demand.

sheets/fig NONE , filed with the letter of _____.

sheets/fig _____ , filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☒ the description, pages NONE .

☒ the claims, Nos. NONE .

☒ the drawings, sheets/fig NONE .

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US97/12677

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. STATEMENT**

Novelty (N)

Claims (Please See supplemental sheet) YESClaims (Please See supplemental sheet) NO

Inventive Step (IS)

Claims (Please See supplemental sheet) YESClaims (Please See supplemental sheet) NO

Industrial Applicability (IA)

Claims (Please See supplemental sheet) YESClaims (Please See supplemental sheet) NO**2. CITATIONS AND EXPLANATIONS**

Claims 1-6, 25, 26, 27-39, 48, 52-66, 73, 117-120 lack novelty under PCT Article 33(2) and lack an inventive step under PCT Article 33 (3) as being anticipated by and obvious over Matsumine et al (Science 272:1020-1023, 1996) as evidenced by Doyle et al. (Cell 85:1067-1076, 1996).

Matsumine et al disclose a composition, a synthetic peptide corresponding to the COOH-terminal 15 amino acids of APC, which inhibits binding between the signal transduction protein, APC and the cytoplasmic protein DLG which contains a GLGF repeat. (See the abstract; page 1020, column 2; page 1021). Matsumine et al do not specifically address the content of the C-terminal amino acids of the signal transduction protein or the synthetic peptide as containing S/T-X-V/I/L, however, it would be inherent that said C-terminal amino acids contain the sequence S/T-X-V/I/L because it was known in the art that these three C-terminal amino acids are critical for PDZ binding as evidenced by Doyle et al (page 1073, column 2, first two paragraphs). Matsumine et al. further disclose methods of identifying the peptide compositions both in vivo and in vitro, by detecting disruption of binding (See page 1020, column 2 into 1021, column 1).

Applicant argues that Matsumine et al. does not anticipate the claimed invention because the peptides of Matsumine et al. require at least 4 C-terminal amino acids while the instant peptides require only 3. This is not found to be persuasive because it is not commensurate in scope with the claimed invention which does not indicate that there is a size limitation nor do the specific examples of peptides limit to 3 C-terminal amino acids. The peptides of Matsumine et al. meet the instant limitations.

Claims 7-24, 40-47, 49-51, 67-72, 74-116 meet the criteria set out in PCT Article 33(2), because the does not explicitly disclose or suggest identification of peptides which induce apoptosis by APC/Fas interactions their use in the treatment of cancer and viral infection.

Claims 1-120 meet the criteria set out in PCT Article 33(4), because the identification of peptides which induce apoptosis by (Continued on Supplemental Sheet.)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US97/12677

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to adequately enable practice of the claimed invention because: The description discloses the identification of peptides that interrupt binding between APC and Fas or other combinations of cytoplasmic and signal transducing proteins having the disclosed sequences. There is no objective evidence, however, rendering it predictable that the administration of such peptides would be reasonably expected to target to the appropriate location and effect apoptosis in cancer or vitally infected cells and thus effectively treat the disease.

Applicant argues that the description lists preferred embodiments of the compositions and provides an example of an inhibition assay of FAs/FAP-1 binding. This argument is not found to be persuasive because the demonstration of *in vitro* activity of a peptide does not supply sufficient objective evidence and guidance regarding its administration and effectiveness *in vivo* to inhibit cancer or viral growth.

Claims 89-120 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not enabled as required under PCT Rule 5.1(a) for the reasons set forth in the immediately preceding paragraph.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US97/12677

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

CLASSIFICATION:~~The International Patent Classification (IPC) and/or the National classification are as listed below:~~

IPC(6): A61K 38/00, 39/00; C07K 1/00, 14/00, 17/00; G01N 33/53, 33/567, 33/574 and US Cl.: 424/198.1; 514/2; 530/351; 435/7.1, 7.23

V. 1. REASONED STATEMENTS:

The report as to Novelty was positive (YES) with respect to claims 7-24, 40-47, 49-51, 67-72, 74-116.

The report as to Novelty was negative (NO) with respect to claims 1-6, 25, 26, 27-39, 48, 52-66, 73, 117-120.

The report as to Inventive Step was positive (YES) with respect to claims 7-24, 40-47, 49-51, 67-72, 74-116.

The report as to Inventive Step was negative (NO) with respect to claims 1-6, 25, 26, 27-39, 48, 52-66, 73, 117-120.

The report as to Industrial Applicability was positive (YES) with respect to claims 1-120.

The report as to Industrial Applicability was negative (NO) with respect to claims NONE.

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

APC/Fas interactions would be useful in the treatment of cancer and viral infection.

____ NEW CITATIONS ____

NONE